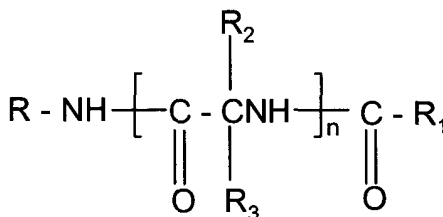


5 **WHAT IS CLAIMED IS:**

1. A method for alleviating pain in a patient suffering from chronic pain comprising administering to said patient an analgesic effective amount of a compound of the formula:

10



*polarity
Reversed*

15

wherein

20 R is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl, aryl lower alkyl, heterocyclic, heterocyclic lower alkyl, lower alkyl heterocyclic, lower cycloalkyl, lower cycloalkyl lower alkyl, and R is unsubstituted or is substituted with at least one electron withdrawing group or electron donating group;

25 R₁ is hydrogen or lower alkyl, lower alkenyl, lower alkynyl, aryl lower alkyl, aryl, heterocyclic lower alkyl, heterocyclic, lower alkyl heterocyclic, lower cycloalkyl, lower, cycloalkyl lower alkyl, each unsubstituted or substituted with an electron donating group or an electron withdrawing group; and

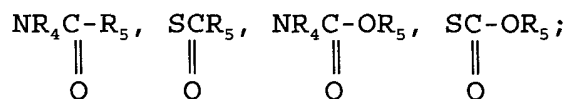
30 R₂ and R₃ are independently hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl lower alkyl, halo, heterocyclic, heterocyclic lower alkyl, lower alkyl heterocyclic, lower cycloalkyl, lower cycloalkyl lower alkyl, or Z-Y wherein R₂ and R₃ may be unsubstituted or substituted with at least one electron

5 withdrawing group or electron donating group wherein the
electron donating group or electron withdrawing group is
acyclic; and wherein heterocyclic in R_2 and R_3 is furyl,
thienyl, pyrazolyl, pyrrolyl, imidazolyl, indolyl,
thiazolyl, oxazolyl, isothiazolyl, isoxazolyl,
10 piperidyl, pyrrolinyl, piperazinyl, quinolyl, triazolyl,
tetrazolyl, isoquinolyl, benzofuryl, benzothienyl,
morpholinyl, benzoxazolyl, tetrahydrofuryl, pyranlyl,
indazolyl, purinyl, indolinyl, pyrazolindinyl,
imidazolinyll, imidazolindinyl, pyrrolidinyl, furazanyl,
15 N-methylindolyl, methylfuryl, pyridazinyl, pyrimidinyl,
pyrazinyl, epoxy, aziridino, oxetanyl or azetidinyll;

Z is O, S, $S(O)_a$, NR_6' , or PR_4 ;

Y is hydrogen, lower alkyl, aryl, aryl lower
alkyl, lower alkenyl, lower alkynyl, heterocyclic,
20 heterocyclic lower alkyl, and Y may be unsubstituted or
substituted with an electron donating group or an
electron withdrawing group, or

ZY taken together is $NR_4NR_5R_7$, NR_4OR_5 , ONR_4R_7 ,
 OPR_4R_5 , PR_4OR_5 , SNR_4R_7 , NR_4SR_7 , SPR_4R_5 , PR_4SR_7 , $NR_4PR_5R_6$ or
25 $PR_4NR_5R_7$,



30 R_6' is hydrogen, lower alkyl, lower alkenyl, or
lower alkynyl and R_4 may be unsubstituted or substituted
with an electron withdrawing group or electron donating
group;

35 R_4 , R_5 and R_6 are independently hydrogen, lower
alkyl, aryl, aryl lower alkyl, lower alkenyl, or lower

5 alkynyl, wherein R_4 , R_5 and R_6 may be unsubstituted or substituted with an electron withdrawing group or an electron donating group; and

10 R_7 is COOR_8 , COR_8 , hydrogen, lower alkyl, aryl, aryl lower alkyl, lower alkenyl or lower alkynyl, which R_7 may be unsubstituted or substituted with an electron withdrawing group or electron donating group;

15 R_8 is hydrogen or lower alkyl, or aryl lower alkyl, and the aryl or alkyl group may be unsubstituted or substituted with an electron withdrawing group or an electron donating group; and

n is 1-4; and

a is 1-3.

2. The method according to Claim 1 wherein one of R_2 and R_3 is hydrogen.

20 3. The method according to Claim 1 wherein n is 1.

4. The method according to Claim 1 wherein one of R_2 and R_3 is hydrogen and n is 1.

25 5. The method according to Claim 1 wherein R is aryl lower alkyl and R_1 is lower alkyl.

6. The method according to Claim 1 wherein

R_2 and R_3 are independently hydrogen, lower alkyl, heterocyclic, heterocyclic loweralkyl, or ZY;

30 Z is O, NR_4 or PR_4 ;

Y is hydrogen or lower alkyl; or

ZY is $\text{NR}_5\text{R}_6\text{R}_7$, NR_5OR_6 , ONR_5R_7 , $\text{NR}_5\text{C}-\text{R}_6$ or $\text{NR}_5\text{C}-\text{OR}_6$.

35 7. The method according to Claim 6 wherein

5 R_2 is hydrogen and R_3 is hydrogen, lower alkyl,
heterocyclic, heterocyclic loweralkyl or ZY;

 Z is O, NR_4 or PR_4 ;

10 Y is hydrogen, lower alkyl; or

 ZY is $NR_5NR_6R_7$, NR_5OR_6 , ONR_5R_7 , $NR_5\overset{\overset{O}{\parallel}}{C}-R_6$ or $NR_5\overset{\overset{O}{\parallel}}{C}-OR_6$.

15

8. The method according to Claim 6 wherein

R_2 is hydrogen and R_3 is lower alkyl, which may
be unsubstituted or substituted with an electron
20 donating or electron withdrawing group, NR_4OR_5 , or ONR_4R_7 .

9. The method according to Claim 8 wherein R_3
is lower alkyl which is unsubstituted or substituted
with hydroxy or loweralkoxy, NR_4OR_6 or ONR_4R_7 , wherein R_4 ,
 R_5 and R_7 are independently hydrogen or lower alkyl, R is
25 aryl loweralkyl, which aryl group may be unsubstituted
or substituted with an electron withdrawing group and R_1
is lower alkyl.

10. The method according to Claim 9 wherein
aryl is phenyl.

30 11. The method according to claim 6 wherein
one of R_2 and R_3 is heterocyclic.

12. The method according to Claim 11 wherein
heterocyclic is heteroaromatic.

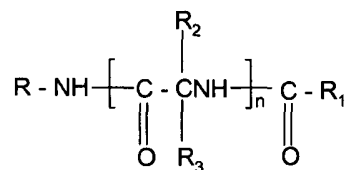
13. The method according to Claim 11 wherein
35 R_3 is furyl, pyridyl, thienyl or thiazolyl.

14. The method according to Claim 9 wherein
aryl is phenyl and is unsubstituted or substituted with
halo.

- 5 15. The method according to Claim 1 wherein
the compound is
 (R) -N-Benzyl-2-acetamide-3-methoxy-
propionamide;
 O-methyl-N-acetyl-D-serine-m-
10 fluorobenzylamide;
 O-methyl-N-acetyl-D-serine-p-
fluorobenzylamide;
 N-acetyl-D-phenylglycinebenzylamide;
 D-1,2-(N, O-dimethylhydroxylamino)-2-acetamide
15 acetic acid benzylamide;
 D-1,2-(O-methylhydroxylamino)-2-acetamido
acetic acid benzylamide.
16. The method according to Claim 1 wherein
the pain is neuropathic pain.
- 20 17. The method according to Claim 6 wherein
the pain is neuropathic pain.
18. The method according to Claim 1 wherein
the pain is nociceptive pain.
19. The method according to Claim 6 wherein
25 the pain is nociceptive pain.
20. A method for the prophylaxis or treatment
of migraine headaches in a subject, comprising
administering to said patient a headache relieving
effective amount of a compound of the formula:

30

5



10 wherein

R is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl, aryl lower alkyl, heterocyclic, heterocyclic lower alkyl, lower alkyl heterocyclic, lower cycloalkyl, lower cycloalkyl lower alkyl, and R is
15 unsubstituted or is substituted with at least one electron withdrawing group or electron donating group;

R₁ is hydrogen or lower alkyl, lower alkenyl, lower alkynyl, aryl lower alkyl, aryl, heterocyclic lower alkyl, heterocyclic, lower alkyl heterocyclic, lower cycloalkyl, lower cycloalkyl lower alkyl, each
20 unsubstituted or substituted with an electron donating group or an electron withdrawing group; and

R₂ and R₃ are independently hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl lower alkyl, aryl, halo, heterocyclic, heterocyclic lower alkyl, lower alkyl heterocyclic, lower alkyl heterocyclic lower cycloalkyl, lower cycloalkyl lower alkyl, or Z-Y wherein
25 R₂ and R₃ may be unsubstituted or substituted with at least one electron withdrawing group or electron donating group;
30

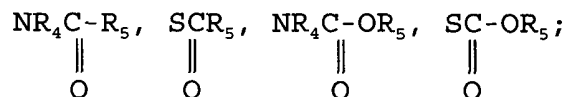
Z is O, S, S(O)_a, NR₄, or PR₄;

Y is hydrogen, lower alkyl, aryl, aryl lower alkyl, lower alkenyl, lower alkynyl, heterocyclic, heterocyclic lower alkyl, and Y may be unsubstituted or

5 substituted with an electron donating group or an
electron withdrawing group, or

ZY taken together is $\text{NR}_4\text{NR}_5\text{R}_7$, NR_4OR_5 , ONR_4R_7 ,
 OPR_4R_5 , PR_4OR_5 , SNR_4R_7 , NR_4SR_7 , SPR_4R_5 or PR_4SR_7 , $\text{NR}_4\text{PR}_5\text{R}_6$ or
 $\text{PR}_4\text{NR}_5\text{R}_7$,

10



15

R_4 , R_5 and R_6 are independently hydrogen, lower
alkyl, aryl, aryl lower alkyl, lower alkenyl, or lower
alkynyl, wherein R_4 , R_5 and R_6 may be unsubstituted or
substituted with an electron withdrawing group or an
electron donating group; and

20

R_7 is COOR_8 or COR_8 , hydrogen, lower alkyl,
aryl, aryl lower alkyl, lower alkenyl or lower alkynyl,
which R_7 may be unsubstituted or substituted with an
electron withdrawing group or electron donating group;

25

R_8 is hydrogen or lower alkyl, or aryl lower
alkyl, and the aryl or alkyl group may be unsubstituted
or substituted with an electron withdrawing group or an
electron donating group; and

n is 1-4;

a is 1-3;

30

wherein

heterocyclic contains from 3 up to 18 ring
atoms and up to a total of 17 ring carbon atoms
containing 1 to 4 hetero ring atoms selected from the
group consisting of nitrogen, oxygen and sulfur.

35

21. The method according to Claim 20 wherein
one of R_2 and R_3 is hydrogen.

5 22. The method according to Claim 20 wherein
n is 1.

23. The method according to Claim 20 wherein
one of R₂ and R₃ is hydrogen and n is 1.

10 24. The method according to Claim 20 wherein
R is aryl lower alkyl and R₁ is lower alkyl.

25. The method according to Claim 20 wherein
R₂ and R₃ are independently hydrogen, lower alkyl, aryl,
aryllower alkyl, heterocyclic, heterocyclic loweralkyl
or ZY;

15 Z is O, NR₄ or PR₄;

Y is hydrogen, lower alkyl, aryl, aryl
loweralkyl, heterocyclic or heterocyclic lower alkyl; or

20 ZY taken together is NR₄NR₅R₇, NR₄OR₅, ONR₄R₇,

NR₄C-R₅, or NR₄C-OR₅; and
 $\begin{array}{c} \parallel \\ \text{O} \end{array}$ $\begin{array}{c} \parallel \\ \text{O} \end{array}$

25 R₄, R₅ and R₇ are independently hydrogen, lower
alkyl, aryl or aryl lower alkyl.

26. The method according to Claim 25 wherein
R₂ is hydrogen and R₃ is lower alkyl, aryl, arylower
30 alkyl, heterocyclic or heterocyclic lower alkyl, or ZY;

Z is O, NR₄ or PR₄;

Y is hydrogen, lower alkyl, aryl, aryl
loweralkyl, heterocyclic or heterocyclic lower alkyl; or

35 ZY taken together is NR₄R₅R₇, NR₄OR₅, ONR₄R₇,

NR₄C-R₅, or NR₄C-OR₅; and
 $\begin{array}{c} \parallel \\ \text{O} \end{array}$ $\begin{array}{c} \parallel \\ \text{O} \end{array}$

R_4 , R_5 and R_7 are independently hydrogen, lower alkyl, aryl or aryl lower alkyl.

27. The method according to Claim 26 wherein
10 R_2 is hydrogen and R_3 is lower alkyl, which may be unsubstituted or substituted with an electron donating or electron withdrawing group, NR_5OR_6 , or ONR_5R_7 .

28. The method according to Claim 26 wherein
15 R_3 is lower alkyl which is unsubstituted or substituted with hydroxy or loweralkoxy, NR_4OR_5 or ONR_4R_7 , wherein R_4 , R_5 and R_7 are independently hydrogen or lower alkyl, R is aryl loweralkyl, which aryl group may be unsubstituted or substituted with an electron withdrawing group and R_1 is lower alkyl.

20 29. The method according to Claim 26 wherein R_3 is heterocyclic.

30. The method according to Claim 29 wherein heterocyclic is heteroaromatic.

25 31. The method according to Claim 30 wherein R_3 is furyl, pyridyl, thienyl or thiazolyl.

32. The method according to Claim 28 wherein aryl is phenyl.

30 33. The method according to Claim 28 wherein aryl is phenyl and is unsubstituted or substituted with halo.

34. The method according to Claim 20 wherein the compound is

(R)-N-Benzyl-2-acetamide-3-methoxy-propionamide;

5 O-methyl-N-acetyl-D-serine-m-
fluorobenzylamide;

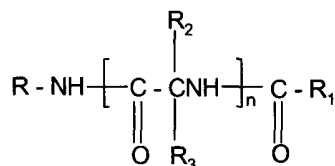
O-methyl-N-acetyl-D-serine-p-
fluorobenzylamide;

N-acetyl-D-phenylglycinebenzylamide;

10 D-1,2- (N, O-dimethylhydroxylamino) -2-acetamide
acetic acid benzylamide; or

D-1,2- (O-methylhydroxylamino) -2-acetamido
acetic acid benzylamide.

35. A method of treating a patient suffering
15 from bipolar disease comprising administering thereto a
therapeutically effective amount of a compound for
treating bipolar disease, said compound having the
formula:



wherein

25 R is hydrogen, lower alkyl, lower alkenyl,
lower alkynyl, aryl, aryl lower alkyl, heterocyclic,
heterocyclic lower alkyl, lower alkyl heterocyclic,
lower cycloalkyl, lower cycloalkyl lower alkyl, and R is
unsubstituted or is substituted with at least one
30 electron withdrawing group or electron donating group;

R₁ is hydrogen or lower alkyl, lower alkenyl,
lower alkynyl, aryl lower alkyl, aryl, heterocyclic
lower alkyl, heterocyclic, lower alkyl heterocyclic,
lower cycloalkyl, lower cycloalkyl lower alkyl, each

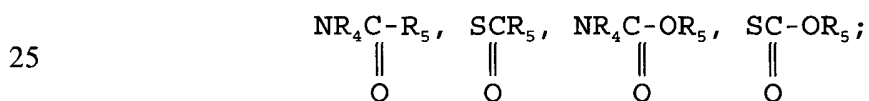
5 unsubstituted or substituted with an electron donating group or an electron withdrawing group; and

R_2 and R_3 are independently hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl lower alkyl, aryl, halo, heterocyclic, heterocyclic lower alkyl, 10 lower alkyl heterocyclic, lower cycloalkyl, lower cycloalkyl lower alkyl, or Z-Y wherein R_2 and R_3 may be unsubstituted or substituted with at least one electron withdrawing group or electron donating group;

Z is O, S, $S(O)_a$, NR_4 , or PR_4 ;

15 Y is hydrogen, lower alkyl, aryl, aryl lower alkyl, lower alkenyl, lower alkynyl, heterocyclic, heterocyclic lower alkyl, and Y may be unsubstituted or substituted with an electron donating group or an electron withdrawing group, or

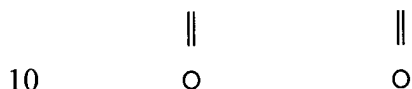
20 ZY taken together is $NR_4NR_5R_7$, NR_4OR_5 , ONR_4R_7 , OPR_4R_5 , PR_4OR_5 , SNR_4R_7 , NR_4SR_7 , SPR_4R_5 or PR_4SR_7 , $NR_4PR_5R_6$ or $PR_4NR_5R_7$,



R_4 , R_5 and R_6 are independently hydrogen, lower alkyl, aryl, aryl lower alkyl, lower alkenyl, or lower 30 alkynyl, wherein R_4 , R_5 and R_6 may be unsubstituted or substituted with an electron withdrawing group or an electron donating group; and

R_7 is $COOR_8$, COR_8 , hydrogen, lower alkyl, aryl, aryl lower alkyl, lower alkenyl or lower alkynyl wherein 35 R_7 may be unsubstituted or substituted with an electron withdrawing group or electron donating group;

5 Y is hydrogen, lower alkyl, aryl, aryl
loweralkyl, heterocyclic or heterocyclic lower alkyl; or
ZY taken together is $\text{NR}_4\text{NR}_5\text{R}_7$, NR_4OR_5 , ONR_4R_7 ,
 $\text{NR}_4\text{C}-\text{R}_5$, or $\text{NR}_4\text{C}-\text{OR}_5$; and



R_4 , R_5 and R_7 are independently hydrogen, lower
alkyl, aryl or aryl lower alkyl.

42. The method according to Claim 41 wherein
15 R_2 is hydrogen and R_3 is lower alkyl, which may
be unsubstituted or substituted with an electron
donating or electron withdrawing group, NR_4OR_5 , or ONR_4R_7 .

43. The method according to Claim 41 wherein
20 R_3 is lower alkyl which is unsubstituted or substituted
with hydroxy or loweralkoxy, NR_4OR_5 or ONR_4R_7 , wherein R_4 ,
 R_5 and R_7 are independently hydrogen or lower alkyl, R is
aryl loweralkyl, which aryl group may be unsubstituted
or substituted with an electron withdrawing group and R_1
is lower alkyl.

25 44. The method according to Claim 41 wherein
 R_3 is heterocyclic.

45. The method according to Claim 44 wherein
heterocyclic is heteroaromatic.

30 46. The method according to Claim 45 wherein
 R_3 is furyl, pyridyl, thienyl or thiazolyl.

47. The method according to Claim 43 wherein
aryl is phenyl.

35 48. The method according to Claim 43 wherein
aryl is phenyl and is unsubstituted or substituted with
halo.

49. The method according to Claim 35 wherein
the compound is (R)-N-Benzyl-2-acetamide-3-methoxy-
propionamide;

O-methyl-N-acetyl-D-serine-m-
fluorobenzylamide;

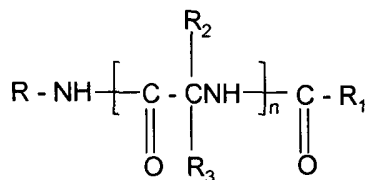
O-methyl-N-acetyl-D-serine-p-
fluorobenzylamide;

N-acetyl-D-phenylglycinebenzylamide;

D-1,2-(N, O-dimethylhydroxylamino)-2-acetamide
acetic acid benzylamide;

D-1,2-(O-methylhydroxylamino)-2-acetamido
acetic acid benzylamide.

50. A method for treating a disorder in a
mammal resulting from abnormal activity at the glycine_o
site of the NMDA receptor in neurons of said mammal
comprising administering to said mammal a
therapeutically effective amount of a compound to
interact with the glycine_o site of the NMDA receptor,
said compound having the formula:



5 wherein

R is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl, aryl lower alkyl, heterocyclic, heterocyclic lower alkyl, lower alkyl heterocyclic, lower cycloalkyl, lower cycloalkyl lower alkyl, and R is
10 unsubstituted or is substituted with at least one electron withdrawing group or electron donating group;

R₁ is hydrogen or lower alkyl, lower alkenyl, lower alkynyl, aryl lower alkyl, aryl, heterocyclic lower alkyl, heterocyclic, lower alkyl heterocyclic, lower cycloalkyl, lower cycloalkyl lower alkyl, each
15 unsubstituted or substituted with an electron donating group or an electron withdrawing group; and

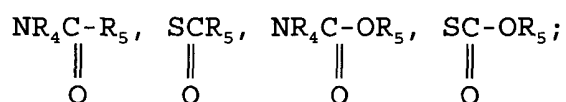
R₂ and R₃ are independently hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl lower alkyl, aryl, halo, heterocyclic, heterocyclic lower alkyl, lower alkyl heterocyclic, lower cycloalkyl, lower cycloalkyl lower alkyl, or Z-Y wherein R₂ and R₃ may be
20 unsubstituted or substituted with at least one electron withdrawing group or electron donating group;

25 Z is O, S, S(O)_a, NR₄, or PR₄;

Y is hydrogen, lower alkyl, aryl, aryl lower alkyl, lower alkenyl, lower alkynyl, heterocyclic, heterocyclic lower alkyl, and Y may be unsubstituted or substituted with an electron donating group or an
30 electron withdrawing group, or

ZY taken together is NR₄NR₅R₇, NR₄OR₅, ONR₄R₇, OPR₄R₅, PR₄OR₅, SNR₄R₇, NR₄SR₇, SPR₄R₅ or PR₄SR₇, NR₄PR₅R₆ or PR₄NR₅R₇,

5



10

R_4 , R_5 and R_6 are independently hydrogen, lower alkyl, aryl, aryl lower alkyl, lower alkenyl, or lower alkynyl, wherein R_4 , R_5 and R_6 may be unsubstituted or substituted with an electron withdrawing group or an electron donating group; and

15

R_7 is COOR_8 or COR_8 , hydrogen, lower alkyl, aryl, aryl lower alkyl, lower alkenyl or lower alkynyl, which R_7 may be unsubstituted or substituted with an electron withdrawing group or electron donating group;

20

R_8 is hydrogen or lower alkyl, or aryl lower alkyl, and the aryl or alkyl group may be unsubstituted or substituted with an electron withdrawing group or an electron donating group; and

n is 1-4; and

a is 1-3.

25

51. The method according to Claim 1 wherein the electron withdrawing group and electron donating group are selected from the group consisting of halo, nitro, carboxy, lower alkenyl, lower alkynyl, formyl, carboxyamido, trifluoromethyl, lower alkoxy carbonyl, hydroxy, lower alkoxy, lower alkyl, amino, lower alkylamino, diloweralkylamino, mercapto, loweralkylthio, and lower alkylidithio.

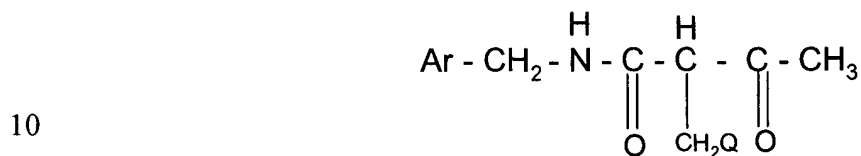
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52. The method according to Claim 20 wherein the electron withdrawing group and electron donating group are selected from the group consisting of halo, nitro, carboxy, loweralkoxy carbonyl, lower alkenyl, lower alkynyl, formyl, aryl, aryl loweralkanoyl,

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5 58. The method of Claim 1 wherein the
compound is of the formula:



wherein

15 Ar is aryl which is unsubstituted or
substituted with an electron donating or electron
withdrawing group, and

Q is loweralkoxy.

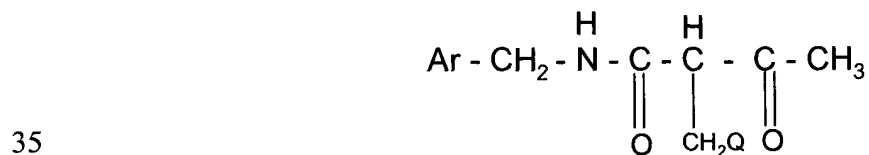
59. The method according to Claim 56 wherein
Ar is unsubstituted aryl or aryl substituted with halo.

20 60. The method according to Claim 56 wherein
Q is methoxy.

61. The method according to Claim 56 wherein
Q is methoxy and Ar is unsubstituted aryl or aryl
substituted with halo.

25 62. The method according to Claim 56 wherein
the carbon atom which is bonded to CH₂Q is in the D
configuration.

30 63. The method according to Claim 20 wherein
Ar is unsubstituted aryl or aryl substituted with halo
wherein the compound has the formula:



5

and Q is lower alkoxy.

64. The method according to Claim 63 wherein Q is methoxy.

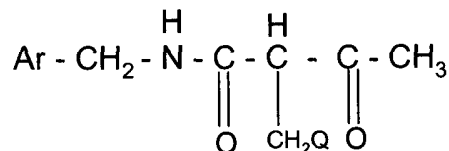
10 65. The method according to Claim 63 wherein Q is methoxy and Ar is unsubstituted aryl or aryl substituted with halo.

66. The method according to Claim 63 wherein the carbon atom which is bonded to CH₂Q is in the D configuration.

15 67. The method according to Claim 63 wherein the carbon atom which is bonded to CH₂Q is in the D configuration.

68. The method of Claim 35 wherein the compound is of the formula:

20



25

wherein

30 Ar is aryl which is unsubstituted or substituted with an electron donating or electron withdrawing group, and

Q is loweralkoxy.

69. The method according to Claim 68 wherein Ar is unsubstituted aryl or aryl substituted with halo.

5 70. The method according to Claim 68 wherein
Q is methoxy.

71. The method according to Claim 68 wherein Q is methoxy and Ar is unsubstituted aryl or aryl substituted with halo.

10 72. The method according to Claim 68 wherein
the carbon atom which is bonded to CH₂Q is in the D
configuration.

[illegible]